Armed Forces College of Medicine

AFCM

Neuroscience Module

Lecture (2)

Amino acid metabolism and brain function

By

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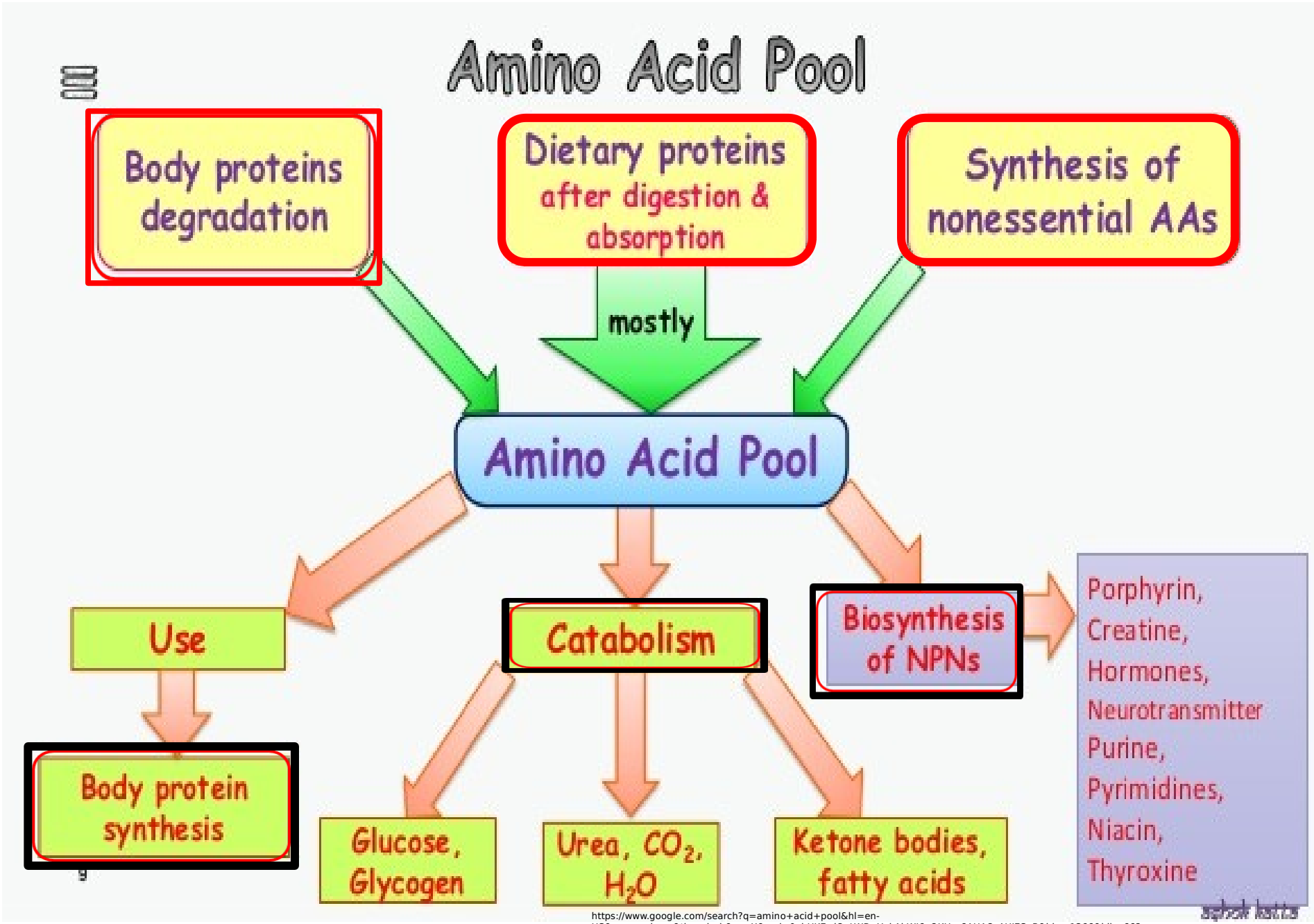
Lecture Key points

- Catabolism of amino acids

INTENDED LEARNING OBJECTIVES (ILO)

By the end of this lecture the student will be able to:

1. Categorize various reactions involved in catabolism of amino acids
2. Illustrate the reaction catalyzed by glutamate dehydrogenase
3. Outline the regulatory mechanisms of glutamate dehydrogenase
4. Justify the clinical significance of transaminases
5. Explain the importance of transamination and decarboxylation reactions to brain function



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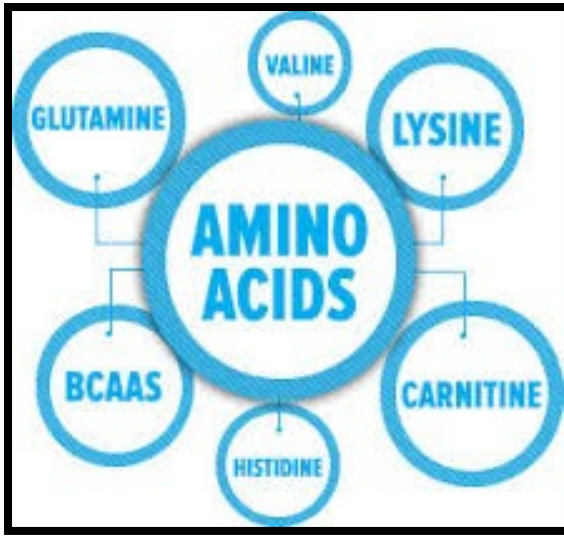
Amino Acids Degradation

Amino acids regardless of their sources, if not incorporated immediate into new proteins, are <u>not stored</u> but rapidly degraded.



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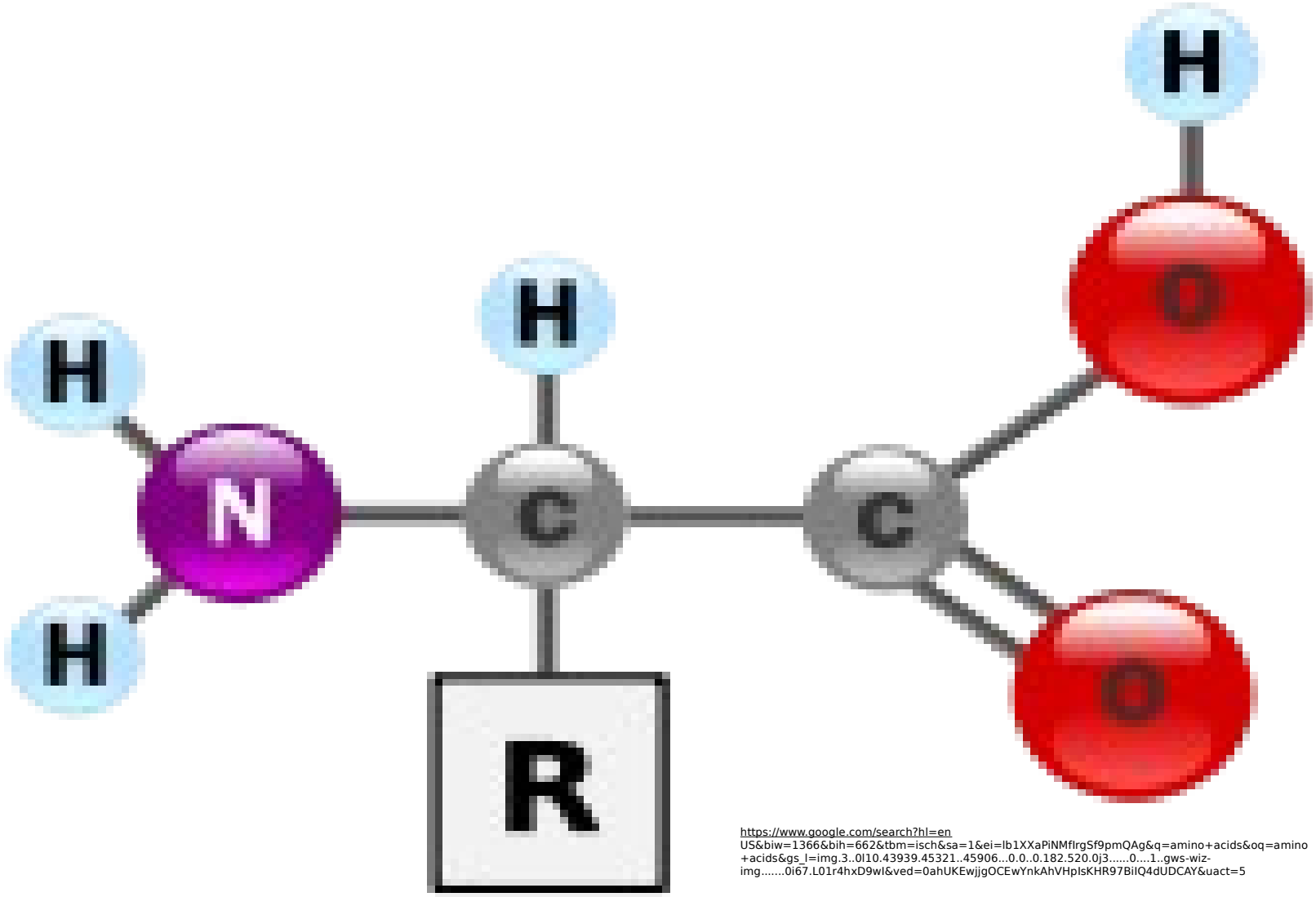

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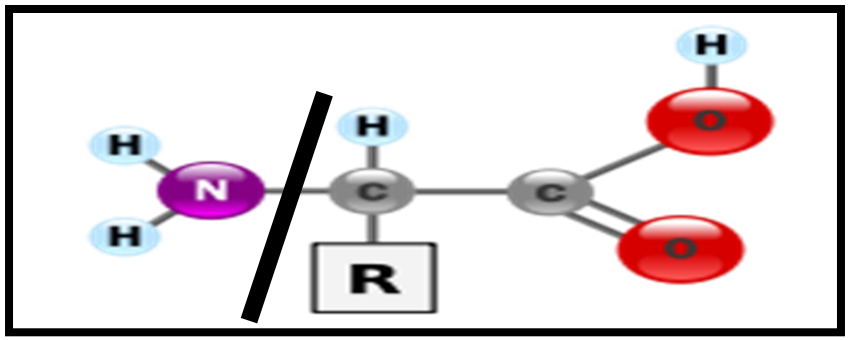
Phases of catabolism of amino acids (1):



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- **<u>A) First phase:</u>**
- 1) the removal of the α-amino groups forming ammonia and the corresponding α-keto acids.

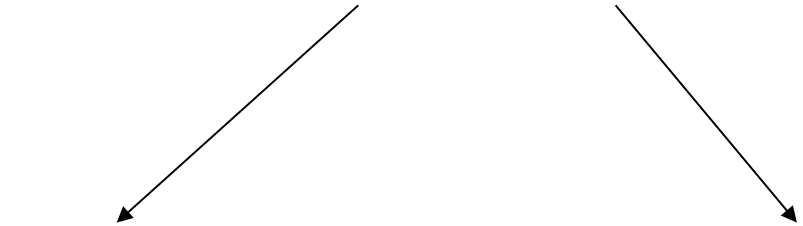
Phases of catabolism of amino acids (2):

- **B) Second phase:**

- The carbon skeletons of the α-keto acids are converted to common intermediates of energy-producing metabolic pathways.

- These compounds can be metabolized to glucose, ketone bodies, fatty acids, CO2 and water.

Catabolism of AAs



- **NH3**
- **urea**
- **Carbon skeleton**
- **Glucogenic fate**
- **Ketogenic fate**
- **Mixed fate**

The carbon skeleton goes to glucose

- **Glucogenic fate**; i.e. synthesis of glucose via gluconeogenesis.

1) Glucogenic AAs

Are AAs whose carbon skeleton yields pyruvate

or

one of the intermediates of TCA cycle

(α-ketoglutarate, oxaloacetate, fumarate, or succinyl CoA).

The carbon skeleton goes to ketone bodies

Ketogenic fate i.e synthesis of KBs
(only leucine & lysine).

2) Ketogenic AAs:

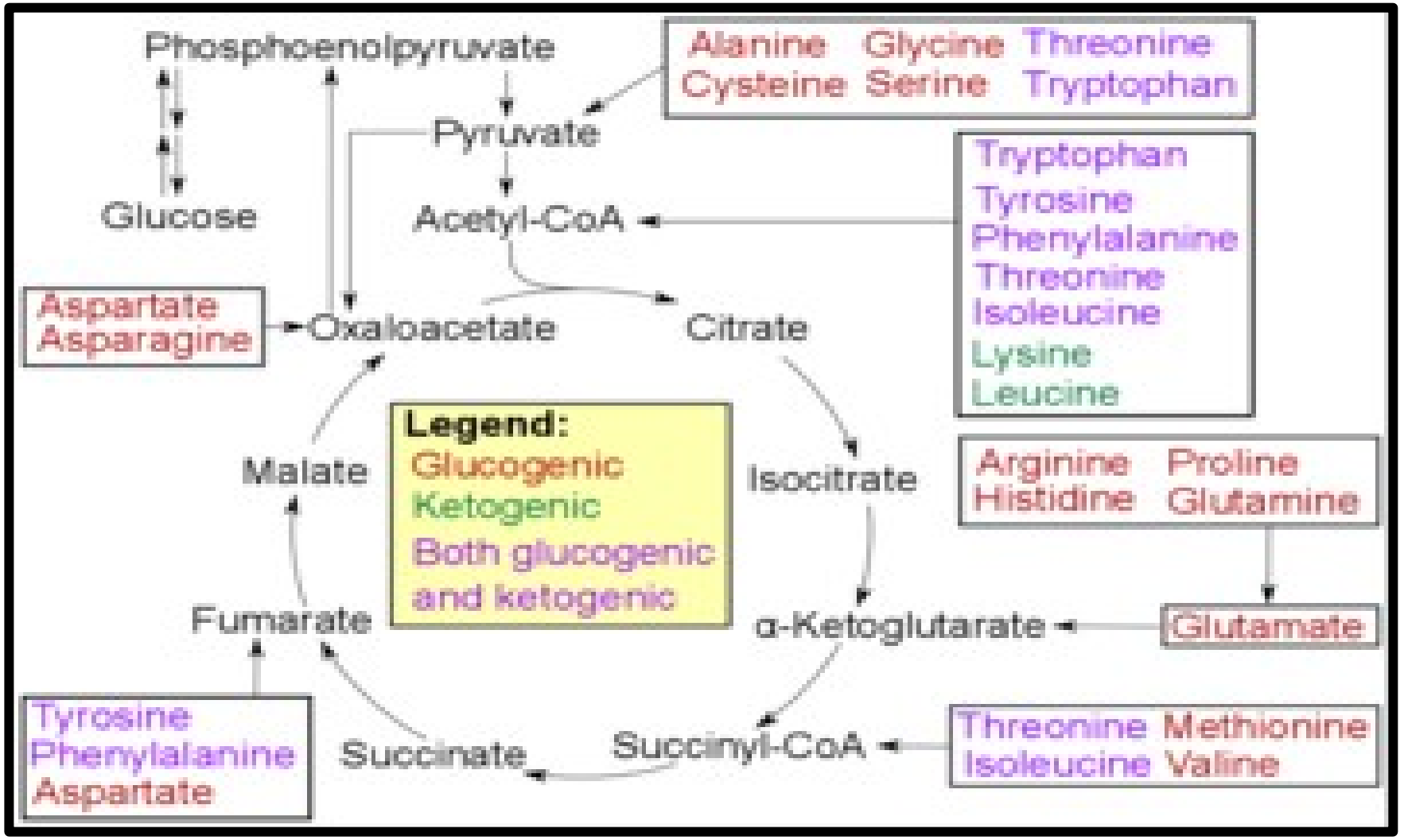
Are AAs whose carbon skeleton yields either Acetyl CoA or Acetoacetayl CoA

The carbon skeleton goes to glucose and ketone bodies

Both glucogenic & ketogenic fate (mixed)

(tyrosine, phenylalanine, tryptophan, threonine and isoleucine).

Fate of amino acids



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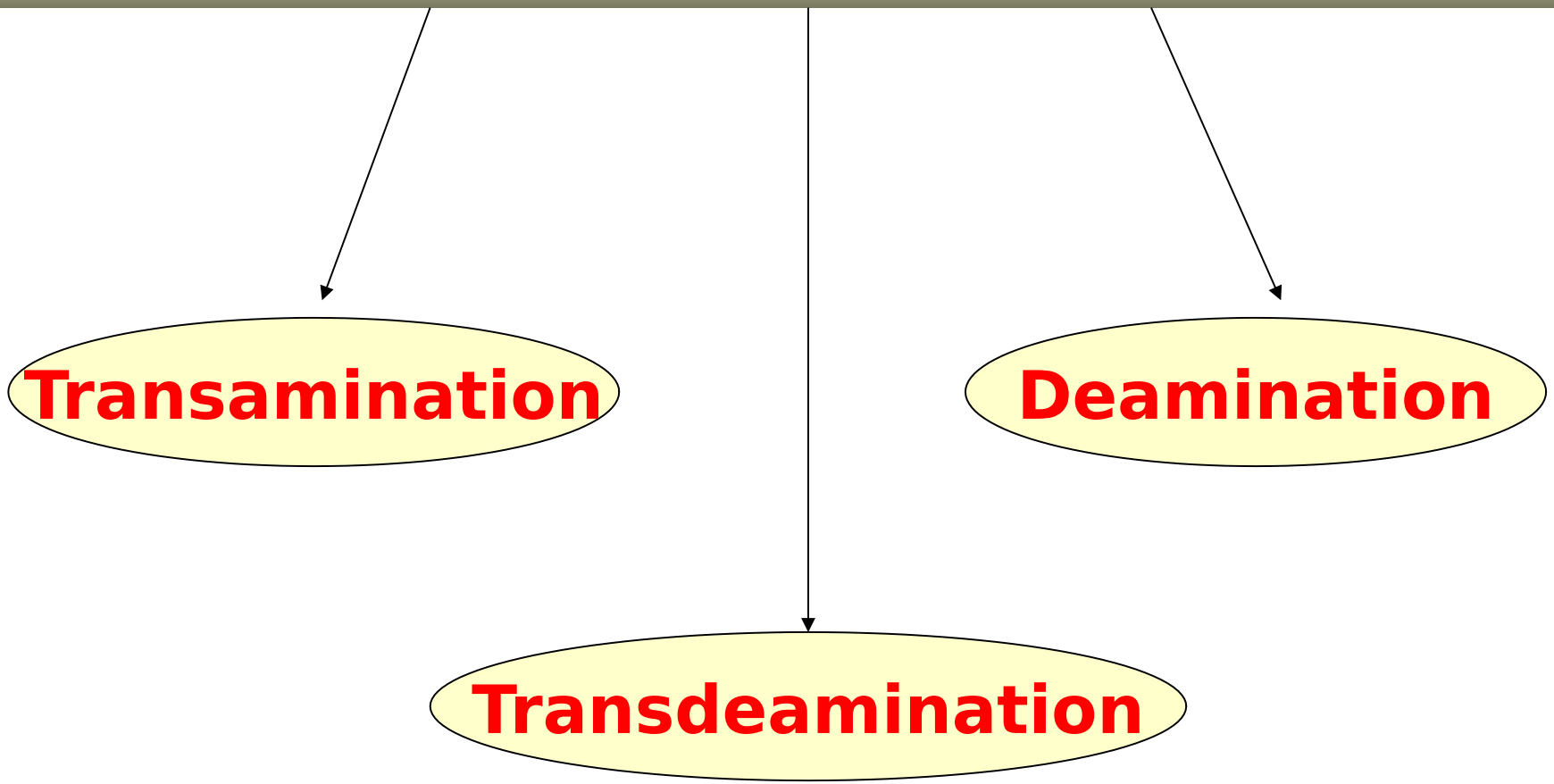
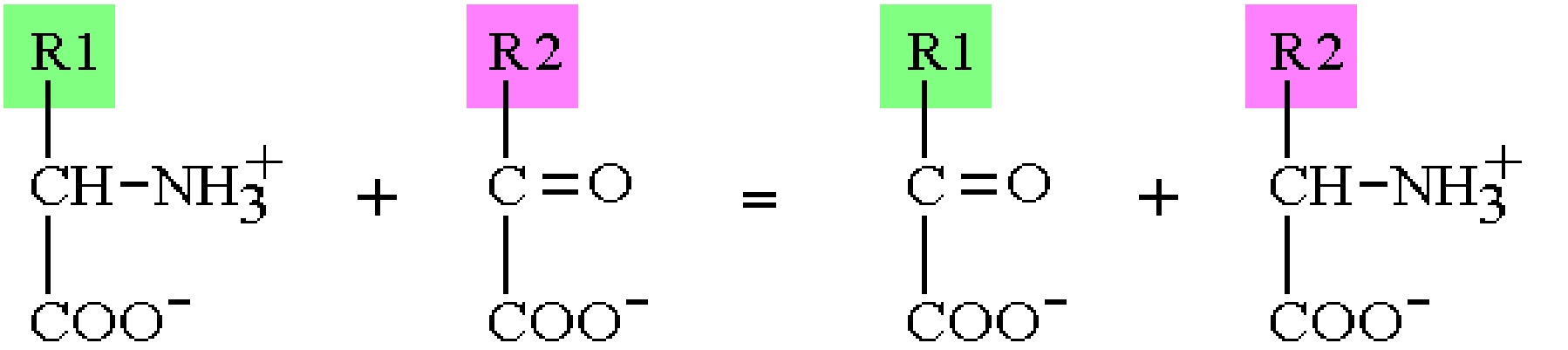
Catabolism of amino acids (Quiz)

- Enumerate glucogenic, ketogenic and mixed amino acids

Catabolic pathways of amino acids



1) Transamination



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Transamination is the transfer of an α-amino group from an α-amino acid to an α-keto acid forming a new amino acid and a new keto acid.

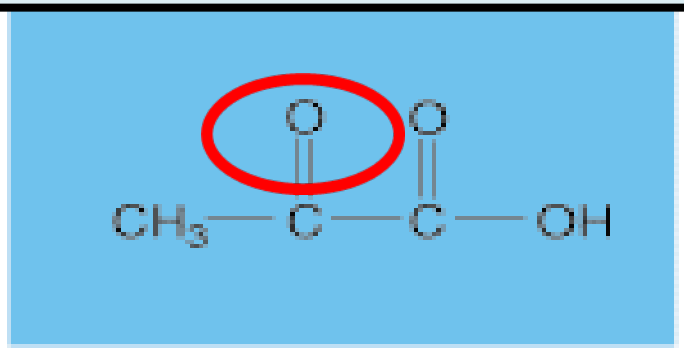
1) Transamination

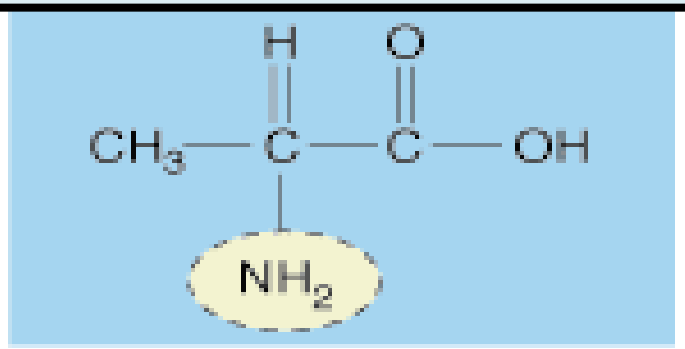
- Carried out by transaminases (aminotransferases)

- Reversible
- They function in both catabolism of AAs & biosynthesis of non-essential AAs

- Their coenzyme is PLP (present at the catalytic site of

Alanine aminotransferase (ALT)
or
Glutamic pyruvic transaminase (GPT)



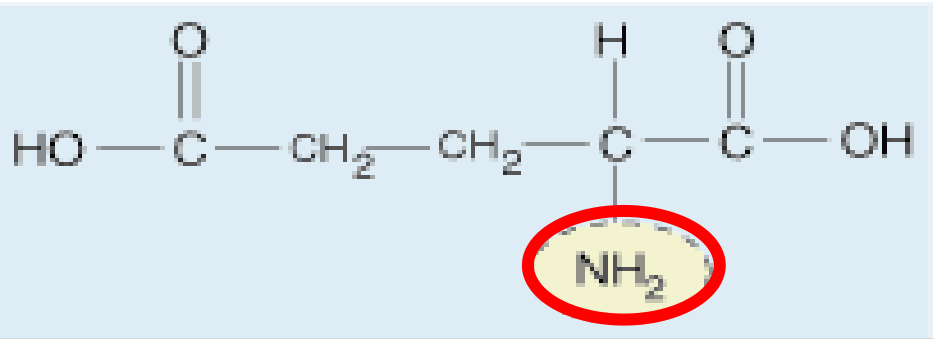


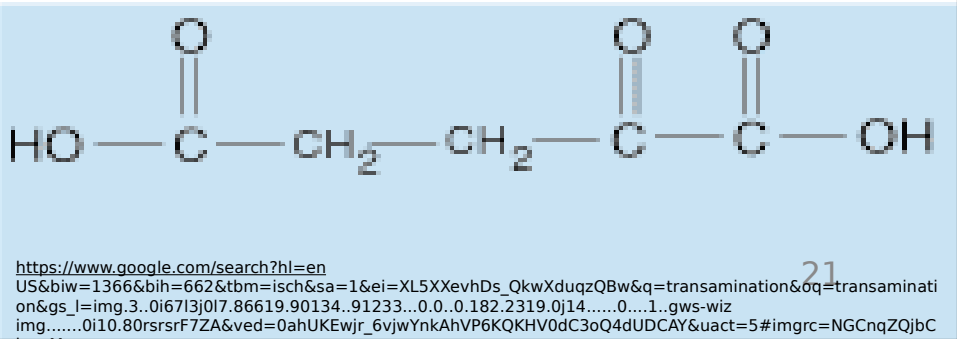
Pyruvic acid

Alanine

Glutamic acid

Alpha-ketoglutaric acid





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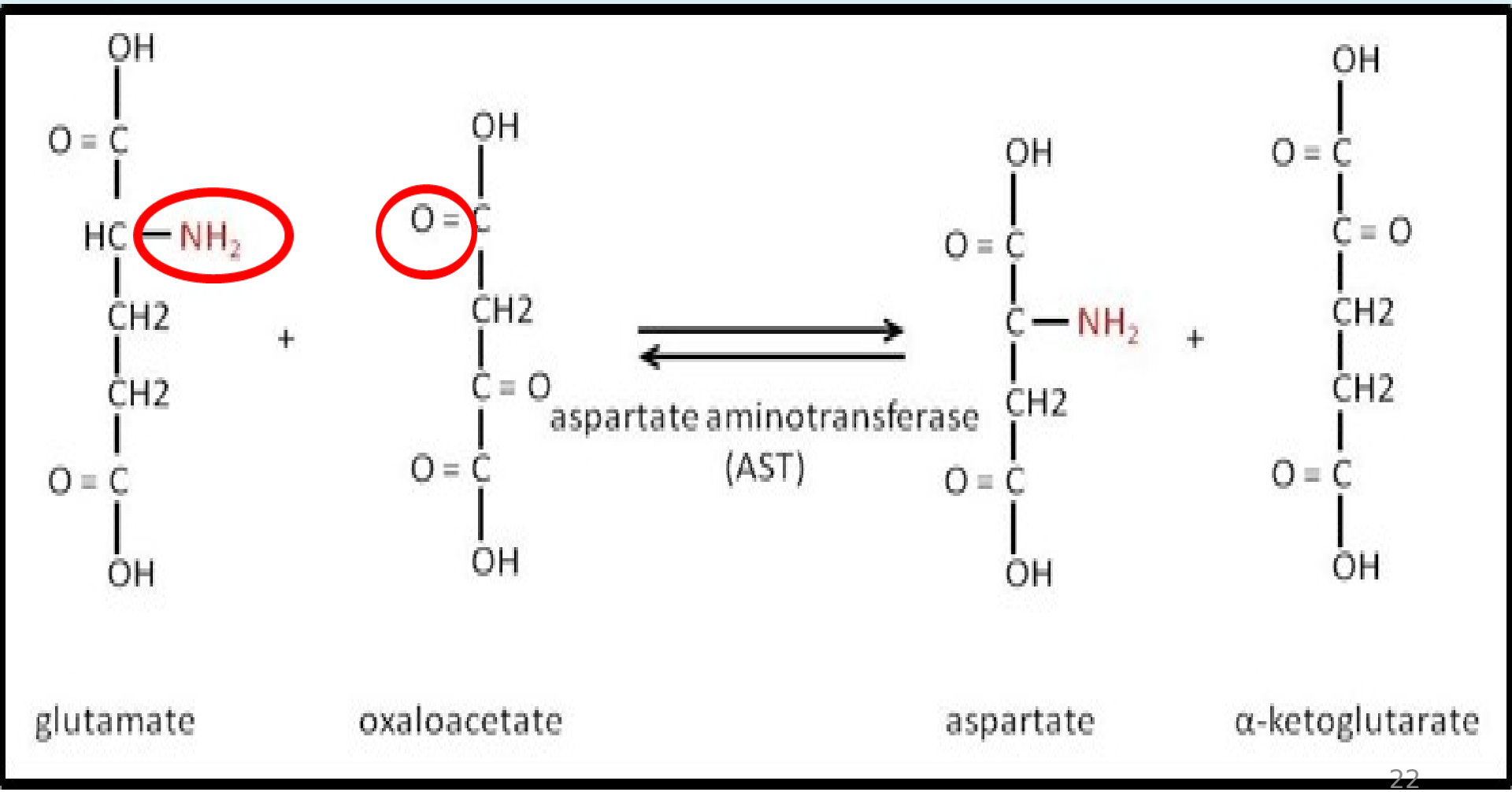
Aspartate aminotransferase (AST) or Glutamic oxaloacetic transaminase (GOT)



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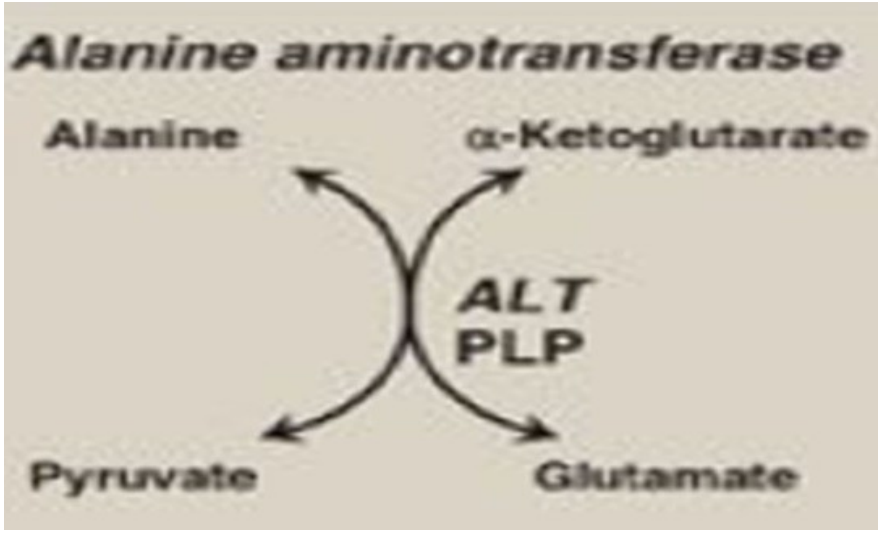
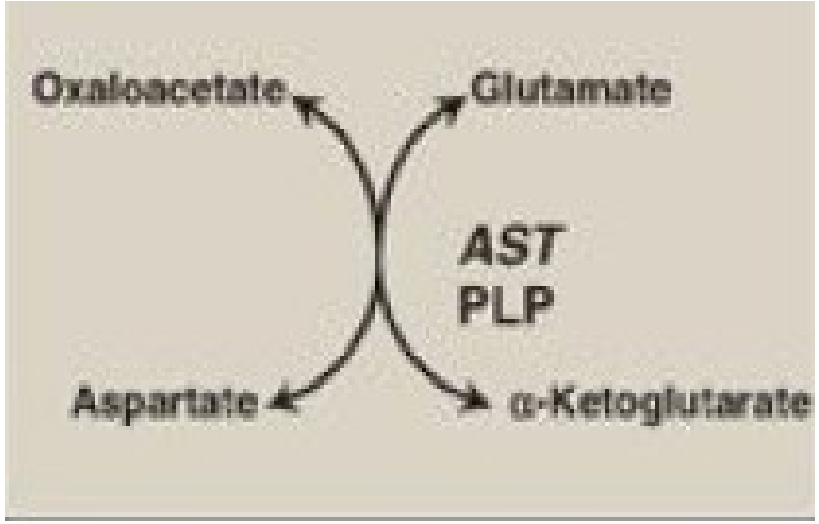
Transaminases (aminotransferases)

Alanine aminotransferase (ALT) or Glutamic pyruvic transaminase (GPT)



Aspartate aminotransferase (AST) or Glutamic oxaloacetic transaminase (GOT)



Lippincott's illustrated reviews in Biochemistry

CLINICAL SIGNIFICANCE OF SERUM TRANSAMINASES

-In liver diseases, there is an increase in both serum ALT (SGPT) and AST (SGOT) levels.

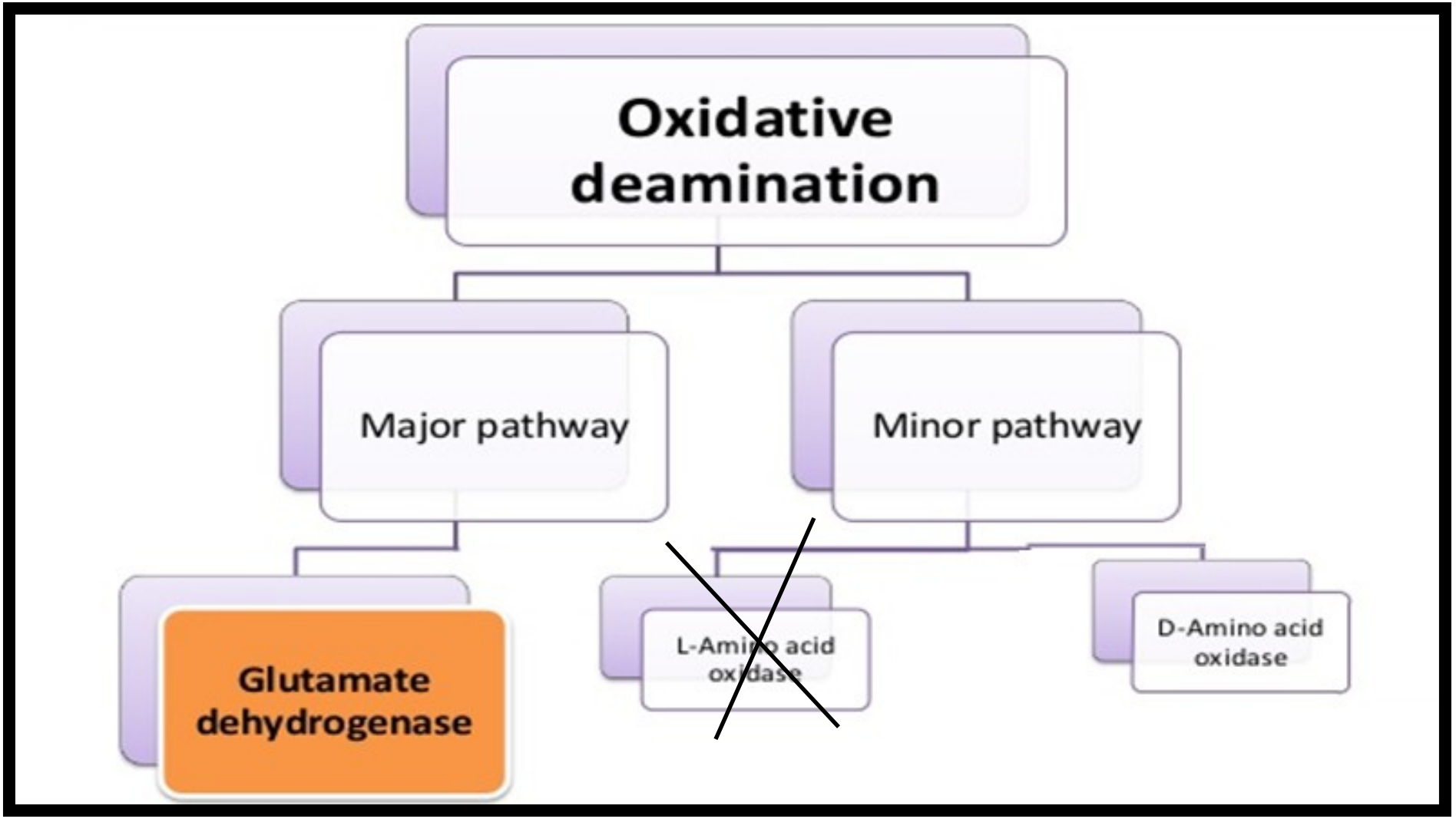
-In heart diseases, e.g. myocardial infarction, there is an increase in SGOT.

-In skeletal muscle diseases, e.g. myasthenia gravis, there is an increase in SGOT.

2) Oxidative Deamination

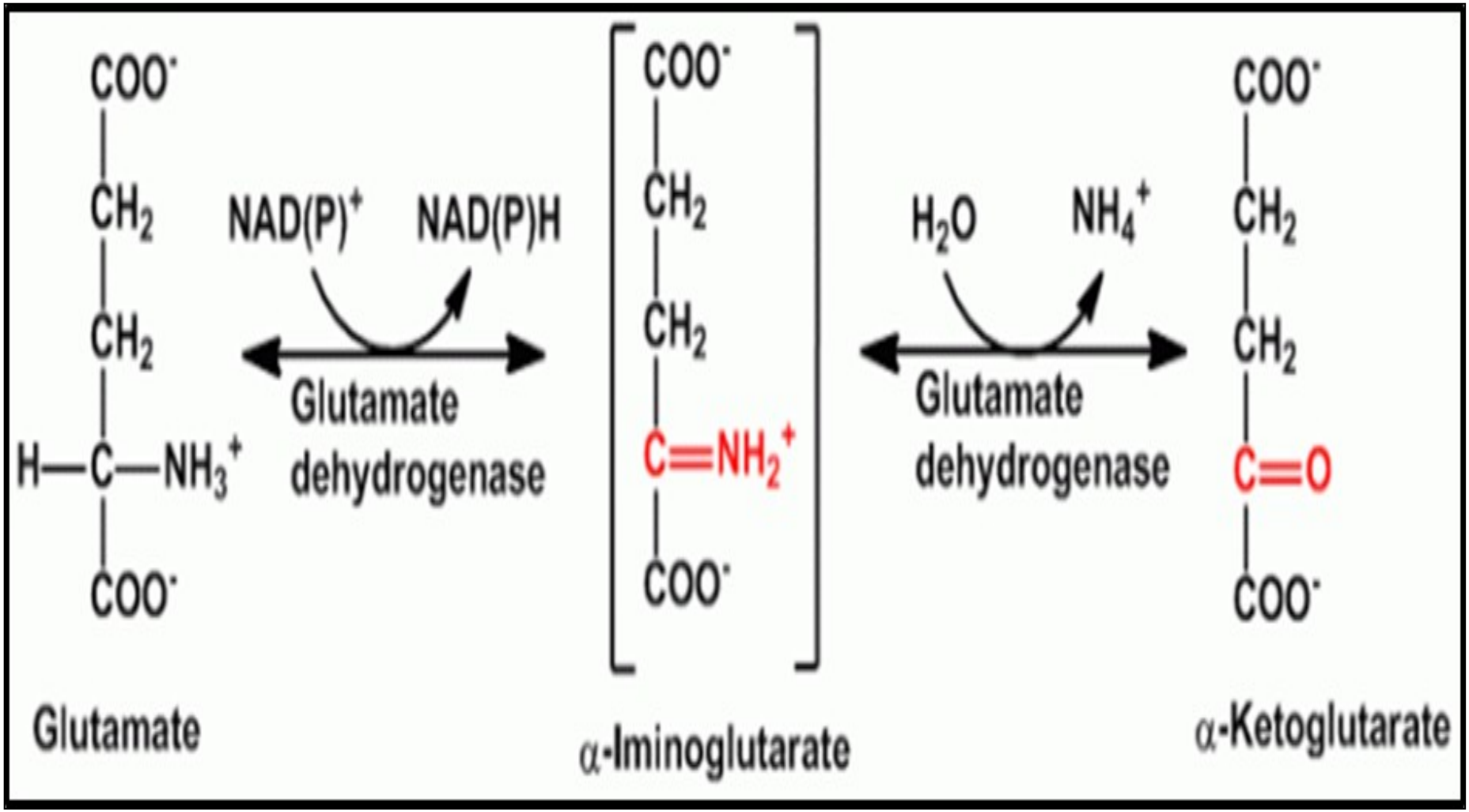
- **It is an oxidative reaction that occurs under aerobic conditions in all tissues but especially the liver and kidney.**

- **During oxidative deamination, the amino group from α-amino acid is removed in the form of ammonia with the formation of α-keto acid.**


Oxidative deamination
Major pathway
Minor pathway
Glutamate dehydrogenase
L-Amino acid oxidase
D-Amino acid oxidase

Glutamate dehydrogenase

-It is present in high concentration in mitochondria of liver, heart, muscles and kidney.



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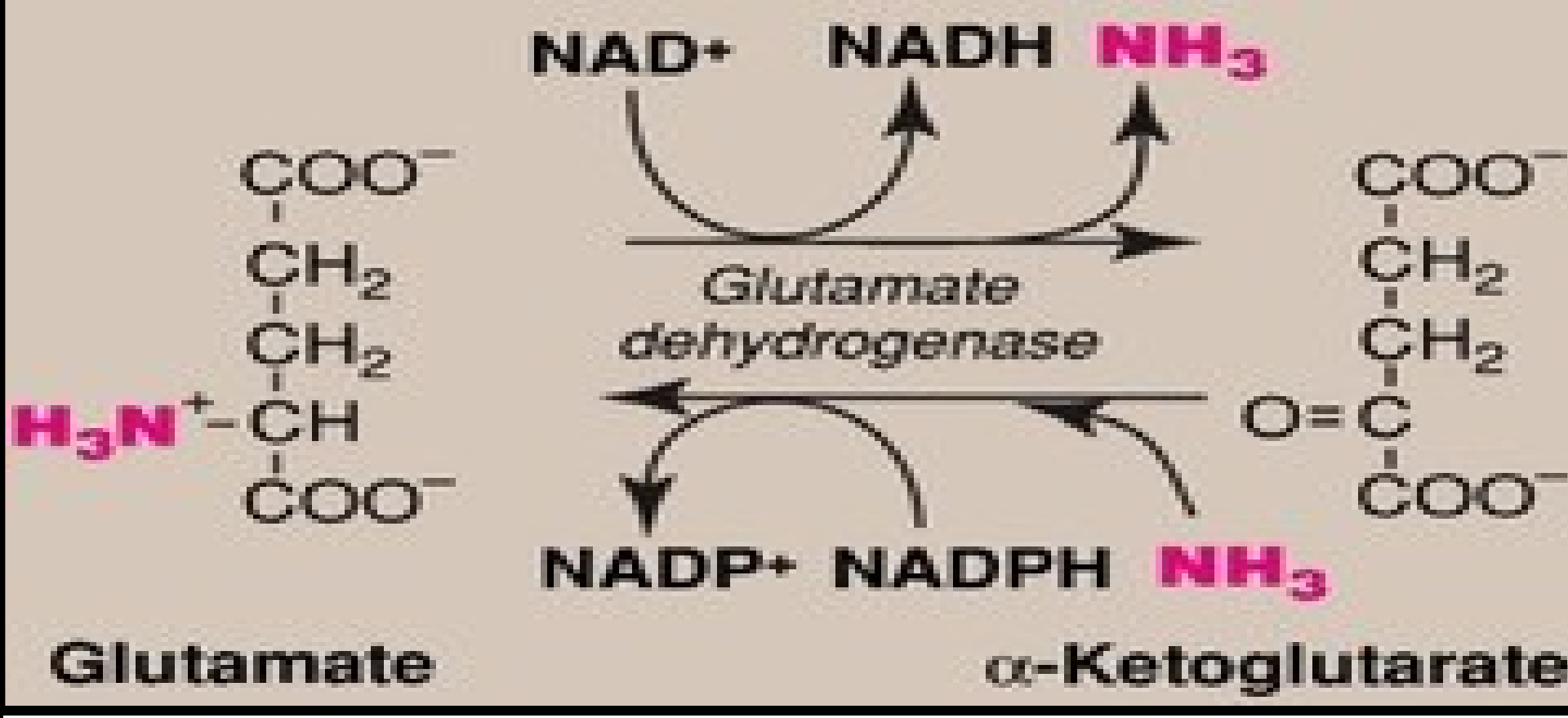
It catalyzes the reversible oxidative deamination of glutamate to α-ketoglutarate and ammonia thus serving in both amino acid catabolism and synthesis

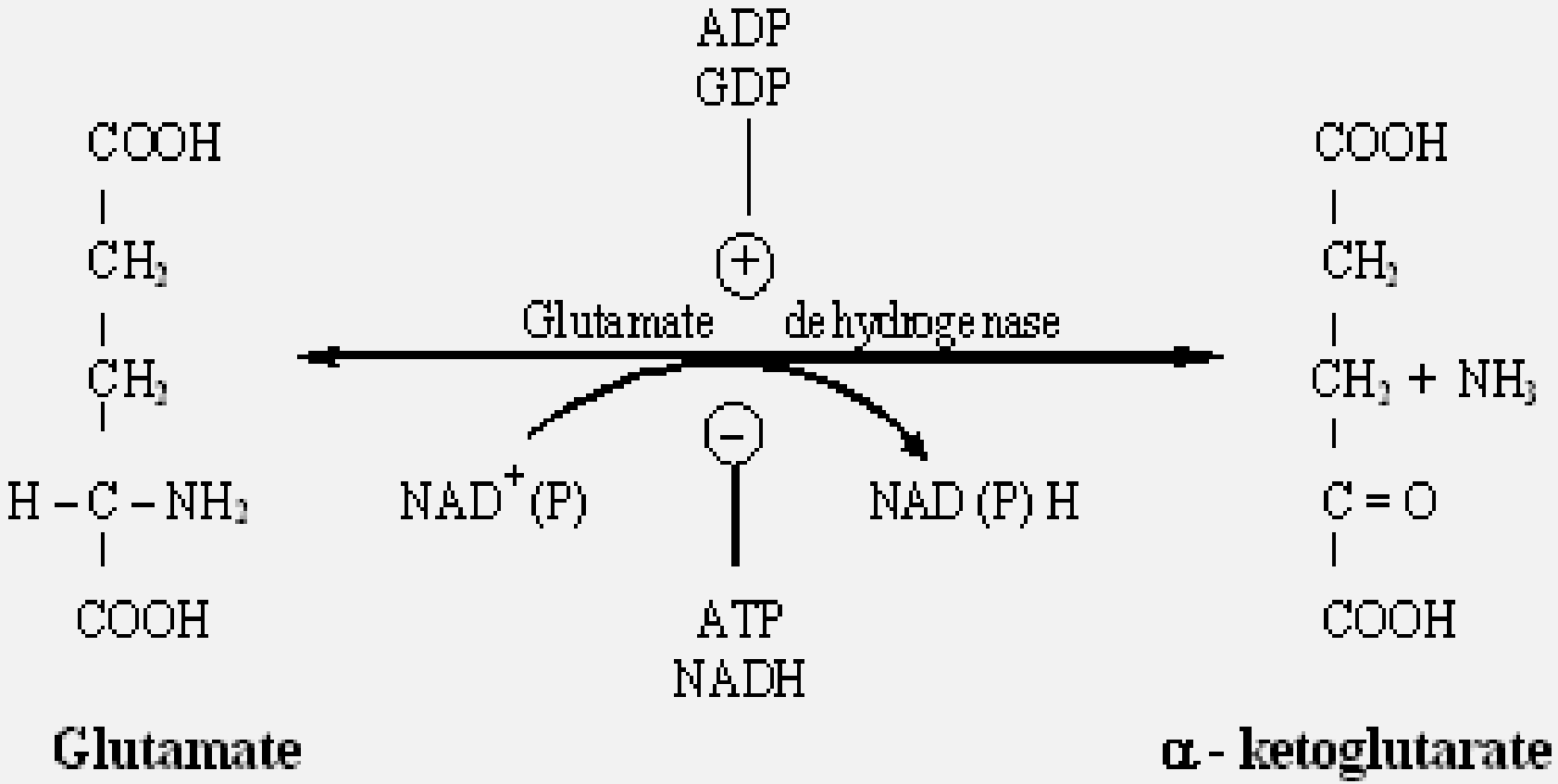


Lippincott's illustrated reviews in Biochemistry (6th edition)

- Glutamate dehydrogenase is a reversible enzyme.
- It needs NAD or NADP as a coenzyme

N.B (NAD+ is used in in oxidative deamination and NADP+ in reductive amination)

Allosteric regulation of Glutamate dehydrogenase



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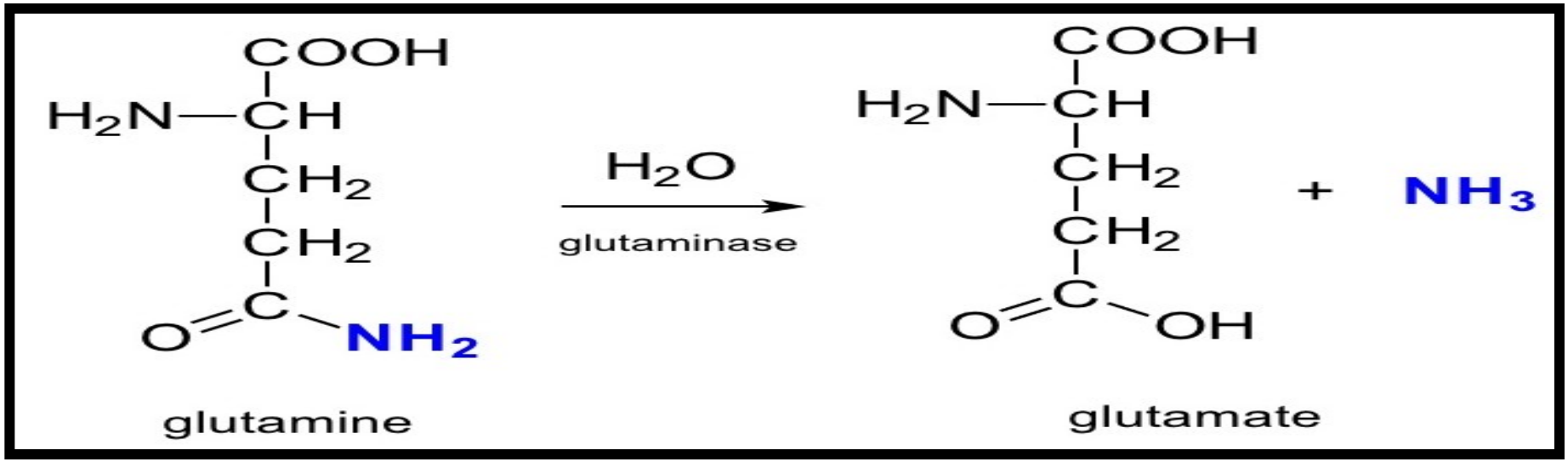
Glutaminases
(Non-oxidative deamination)



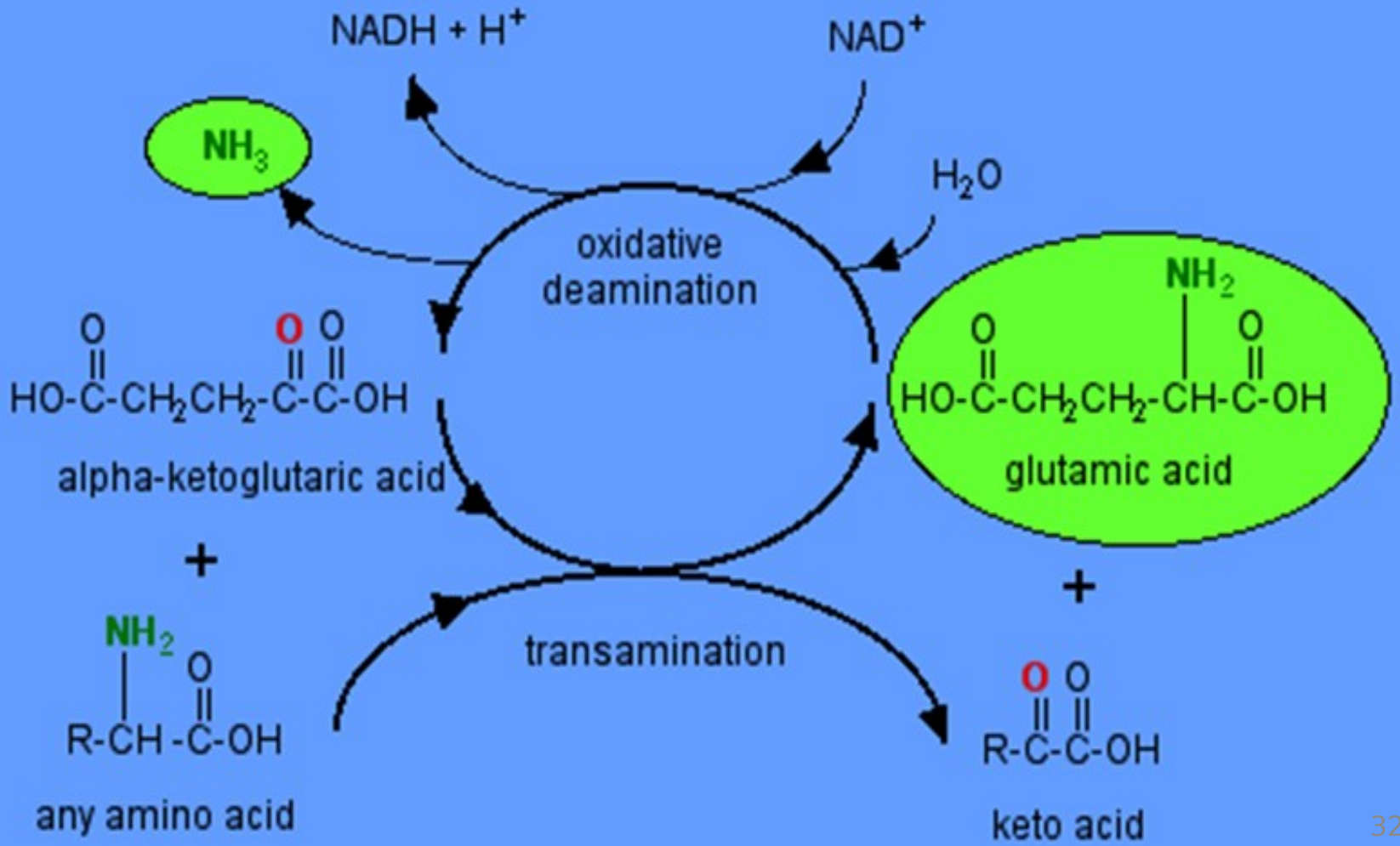
Glutaminases:

N.B

1-In the liver releases NH3→ enters urea cycle

2-In the kidney releases NH3 → passes in urine

3) TRANSDEAMINATION



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Other reactions of AAs not related to AAs catabolism

1) Transmethylation

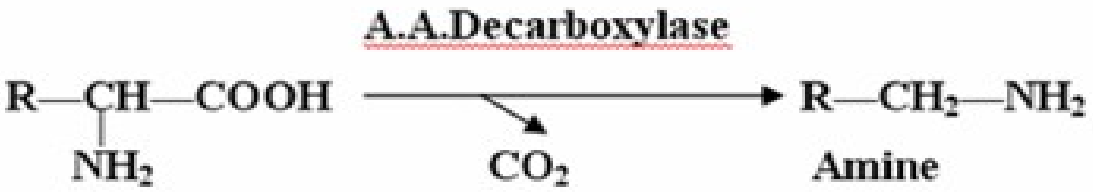
2) Decarboxylation

Importance of these reactions:

Is to obtain important biological active derivatives

Decarboxylation
A) direct decarboxylation

Is the release of CO2 from the COOH group of AAs → corresponding amine



Examples:

Histidine → Histamine

Serine → Ethanolamine

Tyrosine → Tyramine

B) Hydroxylation followed by decarboxylation

Synthesis of

Catecholamines and serotonin

Catabolism of amino acids (Quiz)

USMLE Question

7-year-old girl who presents with a 1-week history of jaundice. The patient's mother reports that, for the past few weeks, the girl has not eaten well and that she has often felt nauseated and has vomited after the few meals that she has eaten. A few days ago, the girl's urine darkened and her stool became pale. On physical examination, the physician notes a fever of 38.5°C (101.3°F), hepatomegaly, jaundice, and icterus. A liver enzyme panel reveals an alanine aminotransferase level of 10,103 IU/ml and an aspartate aminotransferase level of 8030 IU/ml. The patient and her mother deny any illicit drug use or sexual contacts or abuse of the patient. The mother also reports that 1 month ago, two of the girl's playmates had similar symptoms. Which of the following pathogens shares the route of transmission as the pathogen most likely causing this girl's symptoms?

(A) Flavivirus
(B) Hepatitis A virus
(C) Poliovirus
(D) Rabies virus
(E) Varicella-zoster virus

Summary

1) Excess amino acids can not be stored but rapidly degraded.

2) The first phase of catabolism involves the transfer of the α-amino groups through transamination followed by oxidative transamination by glutamate dehydrogenase forming ammonia and the corresponding α-keto acids.

3) Transamination is catalyzed by pyridoxal phosphate-dependent aminotransferases.

4) Most amino acids undergo transamination with α-ketoglutaric acid to form glutamic acid, which in turn is deaminated by glutamate dehydrogenase to form α-ketoglutarate and ammonia.

5) Amino acids are classified into glucogenic, ketogenic and mixed AAs according to the end product of the α-keto acids catabolism.

6) Nitrogen leaves the body as urea, ammonia and other products derived from amino acids metabolism.

SUGGESTED TEXTBOOKS

- **Lippincott's illustrated reviews in Biochemistry by P.C. Champe, R.A. Harvey and D.R. Ferrier**
- **Fundamentals of Clinical Chemistry (Tietz)**
- **"Textbook of Biochemistry with Clinical Correlations" by T.M. Devlin**
- **"Harper's Biochemistry" by R.K. Murray, D.K. Granner, P.A. Mayes and V.W. Rodwell**


THANK YOU